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Microwave Assisted Synthesis of Substituted Coumarinyl Chalcones as Reaction Intermediates for Biologically Important Coumarinyl Heterocycles

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Some of the 5{(substituted and unsubstituted phenyl)-1-phenyl-2-pyrazoline-3"-yl}-6-chloro coumarins were synthesized by the reaction between 3-(3-substituted benzylidine) acetyl 6-chloro coumarin and phenyl hydrazine in presence of pyridine. The former was obtained by treating 3-acetyl-6-chloro coumarin and 3,4,5-trimethyl benzaldehyde. Microwave technology was used at this stage to reduce the reaction time and improve the yield of the product. The resulting compounds were characterized by spectral data and few of the compounds were determined for their partition coefficient and *in vitro* antioxidant properties by DPPH* method. One of the synthesized compounds was found to be a potential candidate for scavenging radical oxygen.

Key Words: Synthesis, Microwave, Coumarin, Pyrazoline, Partition coefficient, Antioxidant property.

INTRODUCTION

The usage of microwave energy to accelerate organic reactions is of increasing interest and offers several advantages over conventional techniques[1]. Synthesis of molecules, which normally require a long time, can be achieved conventionally and rapidly in a microwave oven. In the present study, an attempt was made to synthesize coumarinyl chalcones both by conventional and microwave method.

Coumarin derivatives exhibit a wide spectrum of pharmacological activities such as anticoagulant[2], antimicrobial, antiviral[3], analgesic, anti-inflammatory[4,5] and HIV protease inhibitor[6,7]. Further, substituted pyrazolines were reported for their antibacterial and analgesic activity[8]. Hence, it was proposed to synthesize and characterize 5-{(substituted phenyl)-1-phenyl (2-pyrozoline-3"-yl) substituted coumarin (**10-15**) for their antioxidant activity. Physico-chemical property *i.e.* partition coefficient was also determined for few of the selected test compounds.

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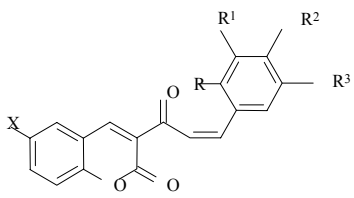
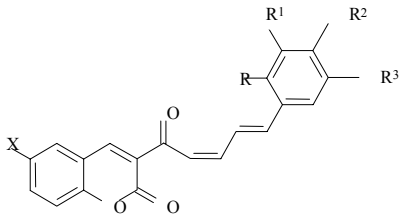
EXPERIMENTAL

Melting points were determined in open capillaries and are found uncorrected. IR spectra were recorded on Fourier transform IR spectrophotometer Model-Shimadzu 8700 using KBr disc method, ^{1}H NMR spectra were recorded on AMX-400 liquid state NMR spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard and mass spectra was recorded on JEOL JMS DX303 Mass spectrometer with Electron Impact Ionization (EII) at 70 ev. The purity of the products was determined by thin layer chromatography. The compounds were analyzed for C, H and N analysis and the values were found within ± 0.4 % of the calculated values. Reaction time and physical data of the products are reported in Tables 1 and 2.

TABLE-1
COMPARISON OF CONVENTIONAL AND MICROWAVE SYNTHESIS OF COUMARINYL CHALCONES



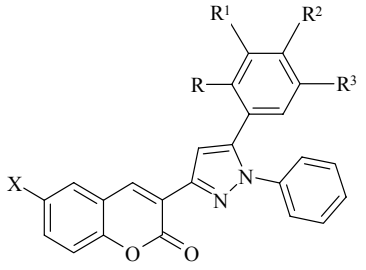
(**4-6**)



(**7 - 9**)

Comp.	X	R	R^1	R^2	R^3	Conventional heating		Microwave irradiation	
						Reaction time (h)	Yield (%)	Reaction time (min)	Yield (%)
4a	H	H	H	$N(CH_3)_2$	H	7	30	3	42
4b	H	Cl	H	H	H	7	27	2	36
4c	H	H	H	OCH_3	H	7	27	2	36
4d	H	H	OCH_3	OCH_3	OCH_3	7	30	3	45
5a	Br	H	H	$N(CH_3)_2$	H	7	26	2	35
5b	Br	Cl	H	H	H	7	30	3	40
5c	Br	H	H	H	H	7	27	3	38
5d	Br	OH	H	H	Br	7	27	3	37
5e	Br	H	OCH_3	OCH_3	OCH_3	7	28	3	41
6a	Cl	H	H	$N(CH_3)_2$	H	7	22	3	37
6b	Cl	Cl	H	H	H	7	26	3	35
6c	Cl	H	H	OCH_3	H	7	25	3	43
6d	Cl	H	OCH_3	OCH_3	OCH_3	7	27	3	42
7	H	H	H	H	H	7	28	2	35
8	Br	H	H	H	H	7	25	2	34
9	Cl	H	H	H	H	7	27	2	36

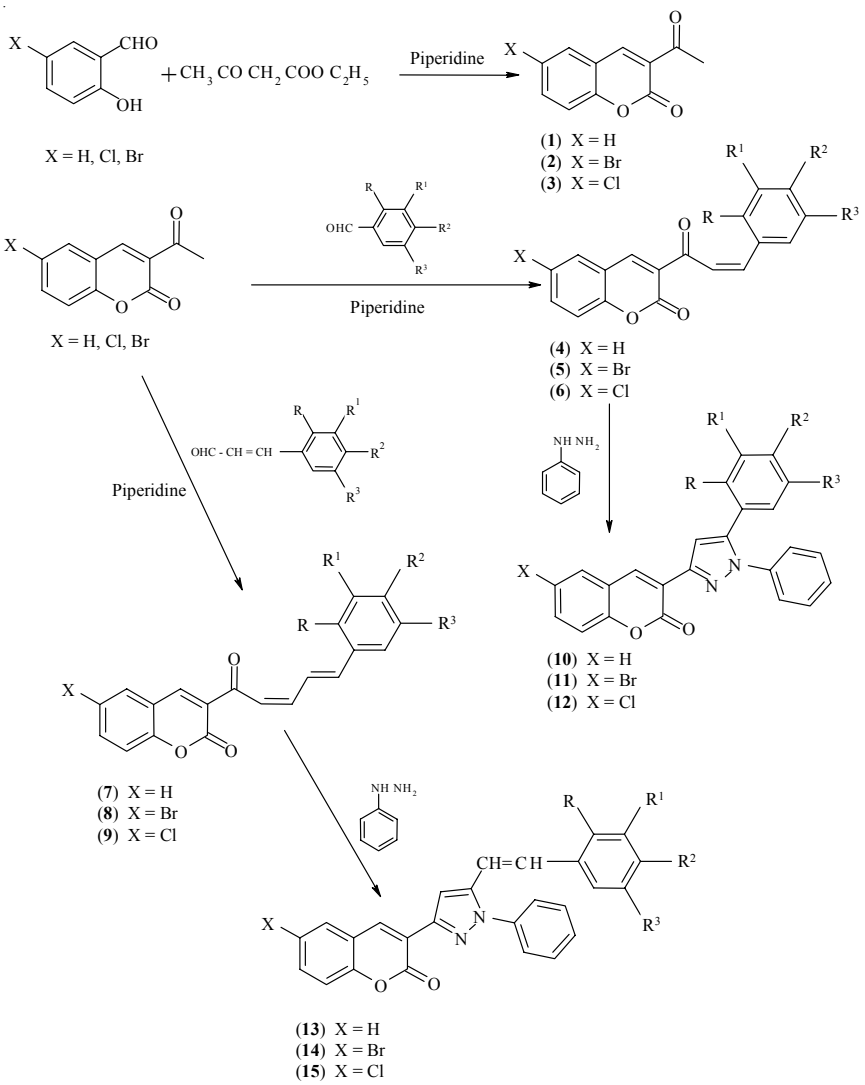
TABLE-2
PHYSICAL DATA OF 5(SUBSTITUTED PHENYL)-1-PHENYL-2-PYROZOLINE-3′′-YL)-6-HALOGEN SUBSTITUTED COUMARINS



Compd.	X	R	R^1	R^2	R^3	Yield (%)	m.p. (ºC)
10a	H	H	H	$N(CH_3)_2$	H	43	160
10b	H	Cl	H	H	H	38	155
10c	H	H	H	OCH_3	H	40	198
10d	H	H	OCH_3	OCH_3	OCH_3	35	184
11a	Br	H	H	$N(CH_3)_2$	H	45	162
11b	Br	Cl	H	H	H	45	160
11c	Br	H	H	H	H	45	162
11d	Br	H	H	H	Br	42	172
11e	Br	H	OCH_3	OCH_3	OCH_3	40	180
12a	Cl	H	H	$N(CH_3)_2$	H	40	180
12b	Cl	Cl	H	H	H	45	160
12c	Cl	H	H	OCH_3	H	50	165
12d	Cl	H	OCH_3	OCH_3	OCH_3	50	135
13	H	H	H	H	H	42	174
14	Br	H	H	H	H	40	164
15	Cl	H	H	H	H	44	167

The syntheses of final compounds (**10-15**) were achieved by cyclization of different substituted coumarinyl chalcones (**4-9**, respectively) with phenyl hydrazine in presence of piperidine. The former compounds were obtained by heating substituted acetyl coumarin and different aromatic aldehyde in ethanol with different time intervals. The synthetic route is shown in **Scheme-I**.

3-Acetyl-6-bromocoumarin (2): To a cooled suspension of mixture of 5-bromosalicylaldehyde (100.5 g, 0.5 mol) and ethylacetoacetate (65 g, 0.5mol), piperidine (10 g) was added with shaking. The mixture was then maintained at freezing temperature for 2-3 h. A yellow coloured lumps which separated out were broken in cold ethanol, filtered and crystallized from hot glacial acetic acid to give needle shaped crystals of (**2**). Yield 94 %, m.p. 220ºC, compound (**1**) was also synthesized by following the same method.



Scheme-I

The formation of acetyl coumarin was confirmed by the difference in m.p., R_f values and specific infrared peaks (cm^{-1}) at 3045 ν(ArC-H), 1730 ν(lactone -C=O), 1700 ν(-C=O), 1610, 1549 ν(ArC=C), 1230 ν(-C-O-), 838, 766 ν(ArC-H) and 563 ν(ArC-Br).

3-Acetyl-6-chlorocoumarin (3): A mixture of 5-chlorosalicylaldehyde (111 g, 0.5 mol) and ethylacetoacetate (65 g, 0.5 mol) were taken in a conical flask, stirred and cooled. To this mixture, piperidine (10 g) was added with shaking. The mixture was then maintained at freezing tempera-

ture for 2-3 h and a yellow coloured solid mass separated out. The lumps were broken in cold ethanol and filtered. The solid was washed with cold ethanol and dried which gave 119 g (75 %) of 3-acetyl-6-chlorocoumarin. The product was recrystallized from hot glacial acetic acid, which yielded needle shape crystals with its m.p. at 219ºC. The formation of this compound was confirmed by the difference in m.p. R_f values and infrared peaks (cm^{-1}) at 3049 ν(ArC-H), 1727 ν(lactone C=O), 1704 ν(-C=O), 1608, 1546 ν(ArC=C), 1226 ν(-C-O-), 833,764 ν(ArC-H) and 564 ν(ArC-Br).

3-(4'-N,N'-Dimethyl amino benzylidine) acetyl-6-bromo coumarin) (conventional method) (5a): A mixture of 3-acetyl 6-bromocoumarin (**2**) (2.67 g, 0.01 mol) and 4-dimethyl amino benzaldehyde (1.49 g, 0.01 mol) in 25 mL ethanol, piperidine (2 g) in 5 mL ethanol was added drop wise. The mixture was heated and refluxed for 7 h. After cooling, the product was separated out and washed with ethanol (20 mL), the product was recrystallized from glacial acetic acid to yield (**5a**). Yield 26 % (1.03 g), m.p. 280ºC. Remaining compounds were also synthesized in a similar manner and shown in Table-1.

General procedure for chalcones preparation by microwave methods: In 250 mL borosil glass beaker, mixture of coumarin (0.01 mol) and aromatic aldehyde (0.01 mol) in 25 mL of ethanol, piperidine (2 g) in 5 mL ethanol was taken, the mixture was heated in microwave at 180 w for 1-4 min (the microwave was stopped between the reactions to ensure that there is no bumping of the solvent). The reaction mixture was then poured in ice-cold water, precipitate obtained was dried and recrystallized from glacial acetic acid.

5-{(4'-N,N'-Dimetyl amino phenyl)-1-phenyl-2-pyrazoline-3''-yl} coumarin (10a): To a mixture of 3-(4'-N,N'-dimethyl amino benzylidine) acetyl coumarin (3.19 g, 0.01 mol) and phenyl hydrazine (1.08 g, 0.01 mol), piperidine (2 g) was added. The mixture was heated and refluxed for 10 h, cooled and poured into crushed ice. The precipitate obtained was filtered and recrystallized from dichloromethane and methanol mixture. Yield was found to be 43 %, with m.p. at 160ºC. Physical properties of remaining compounds are reported in Table-2.

Evaluation of pharmacological activity: Newly synthesized test compounds were subjected for *in vitro* free radical scavenging activity[9] using a method based on the reduction of a methanolic solution of the coloured DPPH* (1,1-diphenyl-2-picryl hydrazyl) radical. The activity was expressed as effective concentration at 50 % reduction (EC_{50}) or the concentration of the test solution required to give a 50 % decrease in absorbance compared to that of blank solution as shown in Table-3.

TABLE-3
DETERMINATION OF PARTITION COEFFICIENT OF 5(SUBSTITUTED PHENYL)-1-PHENYL-2-PYROZOLINE-3´´-YL) 6-HALOGEN SUBSTITUTED COUMARINS

Compound	λ_{max}	Before extraction value (B_E)	After extraction value (A_E)	$P = B_E/B_E\text{-}A_E$	log P
10a	257	1.538	0.125	1.088	0.0366
11a	258	1.430	0.251	1.212	0.0835
12a	257	1.279	0.067	1.055	0.0232
13	257	1.388	0.079	1.060	0.0253
14	257	1.336	0.204	1.200	0.0791

RESULTS AND DISCUSSION

Purity of all the synthesized intermediates and final compounds were checked by their m.p. determination and R_f values of TLC.

Application of microwave energy for intermediates of chalcones preparation significantly proved reduction in the reaction time and the improvement in the product yield.

Randomly selected few of the test compounds such as **10a**, **11a**, **12a**, **13** and **14** showed partition coefficient at 0.0366, 0.0835, 0.0232, 0.0253 and 0.0791, respectively. Presence of an electronegative atom at sixth position on coumarin moiety showed a significant influence on log P values. The average range of log P values for bromo-substituted, chloro-substituted and unsubstituted were found to be 0.0813, 0.0232 and 0.0309, respectively as shown in Table-3. The order of increase in the lipophilicity of coumarinyl pyrazolines was found to be chloro-substituted compounds ≤ unsubstituted < bromo-substituted compounds.

The antioxidant activity of the compounds such as **10c**, **11a**, **12c**, **13** and **15** were performed at random by DPPH* method and was found that only **10c** was found to be a potential candidate for scavenging radical oxygen. The absorbance values of all the five test compounds were shown in Table-4.

TABLE-4
ANTIOXIDANT ACTIVITY OF 5(SUBSTITUTED PHENYL)-1-PHENYL-2-PYROZOLINE-3´´-YL) 6-HALOGEN SUBSTITUTED COUMARINS

Concentration	**10c**	**11a**	**12c**	**13**	**14**
DPPH*	0.90	0.90	0.90	0.90	0.90
20 µL	0.79	0.97	0.54	0.93	0.76
40 µL	0.65	1.14	0.50	1.12	0.93
60 µL	0.42	1.30	0.52	1.24	0.86
80 µL	0.34	0.92	0.90	1.32	0.83
100 µL	0.29	0.70	0.58	1.38	0.77

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